DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA

BLA/Supplement Number:	125197 / 0
Product Name:	PROVENGE® (Sipuleucel-T, APC8015)
Indication(s):	This autologous active cellular immunotherapy product is indicated for the treatment of men with metastatic androgen independent prostate cancer
Applicant:	*Dendreon Corporation*
Date(s):	10/30/09 (date of submission completed) 4/30/10 (due date)
Review Priority:	Priority
Statistical Branch:	TEB/DB
Primary Statistical Reviewer:	Boguang Zhen — Date
Concurring Reviewer (1):	Ghanshyam Gupta — Date
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The large randomized, double-blind, well-controlled Phase III study (D9902B) demonstrated that patients with metastatic androgen independent prostate cancer (AIPC) who received Sipuleucel-T had improvement in overall survival, compared with those who received placebo. The finding was also supported by the other two small randomized trials (D9901, D9902A). Sipuleucel-T appeared to be generally safe and well tolerated by patients with metastatic AIPC.

The efficacy results from the three randomized trials support the claim of using Sipuleucel-T for the treatment of men with asymptomatic or minimally symptomatic metastatic AIPC.

1.2 Brief Overview of Clinical Studies

Dendreon is seeking licensure of Sipuleucel-T (PROVENGE®, APC8015) for the treatment of men with metastatic AIPC. Sipuleucel-T is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein.

In November, 2006, data from Studies D9901 (127 patients) and D9902A (98 patients) under BLA 125197 were submitted. In January 2007, the BLA was accepted for priority review. Study D9901 won the overall survival endpoint, but Study D9902A did not. However, survival endpoint was neither the pre-specified primary endpoint nor the secondary endpoint. At that time, Study D9902B was ongoing. Consequently, a CR letter was sent to the sponsor indicating that more data are needed before the approval of the BLA on May 9, 2007. In particular, results from Study D9902B are needed to provide the most important information for safety and efficacy assessment. In August 2009, results from Study D9902B were submitted under Amendment 33.

Fourteen clinical trials of Sipuleucel-T or related products have been conducted to date. Data to support the efficacy of Sipuleucel-T for the treatment of men with metastatic AIPC are provided from the randomized, double blind, placebo-controlled, multi-center Phase 3 studies D9902B, D9901, and D9902A that enrolled 737 patients, including a total of 488 patients randomized to Sipuleucel-T. Study D9902B is the pivotal trial in this submission and is supported by the results of studies D9901 and D9902A. An improvement in overall survival is the primary evidence of efficacy. Therefore, results of Study D9902B are the primary focus in the evaluation of efficacy of the proposed product. Studies D9901 and D9902A are summarized here and detailed review for these two studies is attached as an appendix to this memo.

Study D9902B was a randomized, double blind, placebo controlled phase 3 trial and was initially concurred under a Special Protocol Agreement in April 2004 with time to objective disease progression as the primary endpoint. Endpoints were later changed to include overall survival as the primary endpoint and time to objective disease progression as the secondary endpoint. These

changes were concurred again under Special Protocol Assessment (SPA) agreement in November 2005. The planned study size was approximately 500 patients and 512 patients were actually enrolled in the study.

1.3 Major Statistical Issues and Findings

Data to support the efficacy of Sipuleucel-T for the treatment of men with metastatic AIPC were provided from the randomized, double blind, placebo-controlled, multi-center Phase 3 studies D9902B, D9901, and D9902A that enrolled a total of 737 patients. Table 1 shows the key efficacy results of the overall survival for the individual studies (D9902B, D9901, and D9902A) and the integrated analysis by pooling all data from the three studies together. A statistically significant improvement in overall survival was observed in Studies D9902B and D9901 though the test of overall survival for Study D9901 was not a pre-specified primary endpoint. A trend towards improvement was observed in Study D9902A. Integrated analysis supports the finding of improvement in overall survival.

Table 1 Summary of Overall Survival Analysis Results

	Sipuleucel-T		Placebo		Sipuleucel-T vs. placebo	
	N	Median Survival[4]	N	Median Survival[4]	Hazard Ratio (95% CI)	p-value
D9902B (N=512)[1]	341	25.8	171	21.7	0.775 (0.614, 0.979)	0.032
D9901 (N=127)[2]	82	25.9	45	21.4	0.586 (0.388, 0.884)	0.010
D9902A (N= 98)[2]	65	19.0	33	15.7	0.786 (0.484, 1.278)	0.331
Integrated Studies (N=737)[3]	488	25.4	249	21.5	0.734 (0.612, 0.881)	0.0009

[1] Hazard Ratio (HR), confidence interval (CI) and p-value estimated according to the primary analysis methods.
[2] HR, CI and p-value estimated based on unadjusted Cox model and log rank test as presented in the individual clinical trial report.
[3] HR, CI and p-value estimated based on Cox model with treatment as independent variable, stratified by study.
[4] Based on a Kaplan-Meier estimate (in months).

No differences between the two study arms were observed in other endpoints. Immune response samples were only collected from a subset of the study population in which, the Sipuleucel-T treated group exhibited some immune-specific responses post-treatment. An improvement in overall survival is the primary evidence of efficacy. The major concern for the observed improvement in overall survival is that the survival difference between the two arms may be attributable to the post-treatment of docetaxel, the only treatment in metastatic castration resistant prostate cancer with a known survival benefit. However, the analyses of docetaxel treatment following randomization did not show that the survival difference between the two arms was attributable to the post-treatment of docetaxel.

Sipuleucel-T, an autologous active cellular immunotherapy product, appeared to be generally safe and well tolerated by patients with metastatic AIPC.

2. INTRODUCTION

2.1 Overview

Dendreon is seeking licensure of Sipuleucel-T (Provenge®, APC8015) for the treatment of men with metastatic AIPC. The claim is based upon analyses comparing overall survival between Sipuleucel-T treated and placebo groups with the relative absence of significant toxicity in this patient population. The proposed target indication for Sipuleucel-T is for the treatment of men with asymptomatic or minimally symptomatic metastatic AIPC.

Sipuleucel-T is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator.

Sipuleucel-T falls into the class of therapies known as active cellular immunotherapies, sometimes termed therapeutic cancer vaccines. Such immunotherapy products are designed to elicit a specific immune response to a target antigen. While the precise mechanism of action is unknown, Sipuleucel-T is designed to induce a cellular immune response targeted against a recombinant fusion protein containing PAP, an antigen expressed in prostate cancer tissue. During ex vivo culture, APCs take up and process the recombinant target antigen into small peptides that are then displayed on the APC surface. In vivo, T cells bind to and recognize the target antigen peptides on the APC surface, eliciting a response characterized by the proliferation and activation of T cells. These activated T cells are the effector cells thought to be responsible for recognition and destruction of prostate cancer cells in vivo. Sipuleucel-T has been shown to stimulate the proliferation of PAP-specific T cell hybridomas in vitro.

In September 2005, Dendreon met with CBER to discuss a proposed Biologic License Application (BLA) for Sipuleucel-T based on the results from the two randomized trials: Studies D9901 and D9902A. In November, 2006, data from Studies D9901 (127 patients) and D9902A (98 patients) under BLA 125197 were submitted. In January 2007, the BLA was accepted for priority review.

On March 29, 2007, the Cell, Tissue and Gene Therapy Advisory Committee met to discuss, whether there was substantial evidence of safety and effectiveness of Sipuleucel-T for the treatment of men with metastatic AIPC. The Committee voted 17-0 to affirm that Sipuleucel-T is reasonably safe for the intended patient population. Furthermore, the Committee voted 13 yes and 4 no that there was substantial evidence of effectiveness. While the Committee voted in favor that the data demonstrated safety and efficacy, the majority of the Committee members felt that efficacy had not been definitively established and that the results from the ongoing trial (Study D9902B) would be critical to answer this question.

Study D9901 showed the overall survival benefit, but Study D9902A did not. However, survival endpoint was neither the pre-specified primary endpoint nor the secondary endpoint. At that time, Study D9902B was ongoing. Consequently, a CR letter was sent to the sponsor on May 9, 2007, indicating that more data are needed before the approval of the BLA. In particular, results from Study D9902B are needed to provide the most important information for safety and efficacy assessment. In August 2009, results from Study D9902B were submitted under Amendment 33, but the 6-month review started on October 30, 2009 when all submissions were complete.

Fourteen clinical trials of Sipuleucel-T or related products have been conducted to date. Data to support the efficacy of Sipuleucel-T for the treatment of men with metastatic AIPC are provided from the randomized, double blind, placebo-controlled, multi-center Phase 3 studies D9902B, D9901, and D9902A that enrolled 737 patients, including a total of 488 patients randomized to Sipuleucel-T. The pivotal study forming the basis of licensure is Study D9902B supported by studies D9901 and D9902A. An improvement in overall survival is the primary evidence of efficacy. Therefore, results of Study D9902B are the primary focus in the evaluation of efficacy of the proposed product. Studies D9901 and D9902A are summarized here and detailed review for these two studies is attached as an appendix to this memo.

2.2 Data Sources

This is a paperless BLA submission. All reports and data were provided electronically and were installed in the Electronic Document Room (EDR) with a STN: 125197\0. Amendment 33 or above can be found by clicking 125197.enx. Data sets and study report for Study D9902B were submitted under Amendment 33. The Integrated Summary of Efficacy and the Integrated Summary of Safety were submitted under Amendment 34.

This reviewer is able to access the study reports, locate and download the data sets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Evaluation of efficacy for Study D9902B is presented in Sections 3.1.1-3.1.4. Some important findings from Studies D9901 and D9902A are summarized in Section 3.1.5 and detailed review for these two studies is attached in an appendix to this memo.

3.1.1 Design and Endpoint (Study D9902B)

Protocol D9902 was conducted in 2 parts: Part A (D9902A) included patients enrolled in the original protocol through Amendment 4 (3/12/2001). D9902A included patients with asymptomatic, metastatic AIPC. Part B (D9902B) commenced with Amendment 5 (5/21/2003) and initially included patients with Gleason sum ≤ 7 malignancies only. Beginning with Amendment 7 (10/11/2005), patients were enrolled regardless of Gleason sum, and minimally symptomatic patients, in addition to asymptomatic patients, were eligible for enrollment. Studies D9902A and D9902B were analyzed separately. The results of Study D9902A were submitted as part of a Biologics License Application (BLA) to FDA for review under BLA STN 125197/0 in August 2006. In August 2009, results from Study D9902B were submitted under Amendment 33.

Study D9902B is a randomized, double blind, placebo controlled phase 3 trial to evaluate the efficacy and safety of Sipuleucel-T in asymptomatic or minimally symptomatic patients with metastatic AIPC.

D9902B protocol was initially concurred under a Special Protocol Agreement in April 2004 with time to objective disease progression as the primary endpoint. Endpoints were later changed to include overall survival as the primary endpoint and time to objective disease progression as the secondary endpoint. These changes were concurred again under SPA agreement in November 2005.

The planned study size was approximately 500 patients. The study was designed for 88% power at $\alpha = 0.05$, assuming a hazards ratio (HR) for death of 0.69 (Sipuleucel-T versus placebo). Patients were evaluated for eligibility, stratified by primary Gleason grade (≤ 3, ≥ 4), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no), and then randomized in a 2:1 ratio to receive Sipuleucel-T (active treatment group) or placebo (control group). A centralized, minimization method was employed in an attempt to balance the two treatment groups by the three stratification factors. Following randomization, patients from both treatment groups were scheduled to undergo a series of 3 leukapheresis procedures (at approximately Weeks 0, 2, and 4), each followed 2 to 3 days later by infusion of Sipuleucel-T or placebo.

The trial enrollment criteria

1. Written informed consent obtained prior to the initiation of study procedures.

2. Histologically documented adenocarcinoma of the prostate.

3. Metastatic disease as evidenced by soft tissue and/or bony metastases on baseline bone scan and/or computed tomography (CT) scan of the abdomen and pelvis.

4. Castration resistant prostate cancer: patients had current or historical evidence of disease progression concomitant with surgical or medical castration, as demonstrated by PSA progression OR progression of measurable disease OR progression of non-measurable disease as defined below:

    - PSA: Two consecutive PSA values, at least 14 days apart, each ≥ 5.0 ng/mL and ≥ 50% above the minimum PSA observed during castration therapy or above the pre-treatment value if there was no response.

    - Measurable disease: ≥ 50% increase in the sum of the cross products of all measurable lesions or the development of any new lesions. The change was measured against the best response to castration therapy or against the pre-castration measurements if there was no response.

    - Non-measurable disease: Soft tissue disease -- The appearance of 1 or more new lesions, and/or unequivocal worsening of non measurable disease when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response; Bone disease -- Appearance of 2 or more new areas of abnormal uptake on bone scan when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response. Increased uptake of pre-existing lesions on bone scan did not constitute progression.

5. Serum PSA ≥ 5.0 ng/mL.

6. Castrate levels of testosterone (< 50 ng/dL) achieved via medical or surgical castration. Surgical castration must have occurred at least 3 months prior to registration. Patients who were not surgically castrate must have received medical castration therapy, have initiated such therapy at least 3 months prior to registration, and must have continued such therapy until the time of confirmed objective disease progression.

7. Life expectancy of at least 6 months.

8. Men ≥ 18 years of age.

9. Adequate hematologic, renal, and liver function.

10. Negative serology tests for human immunodeficiency virus (HIV) 1 and 2, human T cell lymphotropic virus (HTLV)-1, and Hepatitis B and C.

Primary Endpoint: Overall Survival

Overall survival was defined as the time from randomization to death due to any cause. Those

patients without reported death events by the data cut-off date were censored at the date of their last documented study evaluation or contact date (when the patient could be confirmed to be alive), whichever was later. If such date was beyond the data cut-off date, the patient was censored at the data cut-off date. Overall survival time was calculated as follows:

- For patients who died
  Survival time (days) = [(death date) – (randomization date)] + 1

- For patients who were censored
  Survival time (days) = [(maximum (last study visit date, last contact date)) – (randomization date)] + 1

Secondary Endpoint: Time to Objective Disease Progression

Time to objective disease progression was defined as the time from randomization to achieving objective disease progression, as determined by the Independent Radiology Review Committee (IRRC) for the study. Patients who had not demonstrated objective disease progression prior to the data cut-off date were censored at the time of their last imaging visit date obtained per protocol, unless they died prior to attaining objective disease progression in which case they were considered to be competing events. Nonprotocol specified imaging studies such as magnetic resonance imaging (MRI) scans, ultrasound exams, and x-rays were not included for this analysis. Patients who were lost to follow-up, withdrew consent, or discontinued follow-up prior to confirmed objective disease progression were censored at their last imaging visit date. The IRRC provided the date of objective disease progression. If the progression event could not be determined by IRRC reviewers, the patient was considered to be without objective disease progression.

Tertiary Endpoints:

Time to clinical progression was defined as the time from randomization to clinical disease progression. Patients who had not demonstrated clinical disease progression prior to the analysis were censored at the time of their last clinical assessment (i.e., clinical study visit or imaging study, whichever occurred later). A death event prior to clinical progression was analyzed as a competing event.

PSA Doubling Time: The population PSA time slope (or PSA velocity) for each treatment arm was computed based on a mixed effects model with all PSA measurements from baseline until the institution of other systemic anticancer therapy. The response variable was the log transformed PSA. The fixed effects included stratification factors, time (as a continuous variable), treatment, and treatment by time interaction. Patients were considered as a random effect.

Immune Response: Antigen-specific humoral and cellular immune responses were assessed before (Week 0) and after treatment (Weeks 6, 14, and 26, and at the post-progression follow-up [PPFU] visit) in both Sipuleucel-T and placebo patients. Humoral responses to PA2024, PAP, and GM-CSF were assessed by enzyme-linked immunosorbent assay (ELISA) in cryopreserved patient serum. Cellular responses to PA2024 and PAP were assessed by interferon gamma enzyme- linked immunosorbent spot (ELISPOT) assays, as well as T cell proliferation assays

incorporating tritiated-thymidine (3H-thymidine). Due to sample availability issues, not all patients could be evaluated for immune responses. Prior to Protocol Amendment 7, immune response samples were only collected from patients at clinical trial sites in close proximity to the -b(4)--- Cell Processing Center.

3.1.2 Statistical Methodologies (Study D9902B)

The primary analysis of overall survival used Wald's test (2-sided) for treatment effect based on a stratified Cox regression model with treatment, adjusted for 2 baseline covariates (PSA [natural log (ln)] and LDH [ln]), stratified by the randomization factors of primary Gleason grade (≤ 3, ≥ 4), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no). The null hypothesis would be no difference in overall survival between treatment groups (HR = 1).

The primary analysis included all randomized patients (ITT population). Patients with missing covariates were imputed by the median of the data collected from patients without the missing value. An analysis based only on patients without any missing baseline covariates (PSA and LDH) was conducted to support the primary analysis.

The estimated HR of the treatment effect and its 2-sided, 95% confidence interval (CI), using the placebo arm as the denominator, was generated based on the same Cox regression model described above. The Kaplan-Meier method was used to estimate the overall survival distribution.

The final analysis was planned to be conducted when 304 death events occur. The interim analysis was conducted based on a data cut-off date of 28 MAY 2008, when 247 death events had been observed. Therefore, the actual significance level for the final analysis was adjusted to 0.043.

For the secondary endpoint, time to objective disease progression, the 2-sided p-value associated with the treatment effect using the log rank test stratified by primary Gleason grade (≤ 3, ≥ 4), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no) was calculated to assess the treatment effect. The stratified Cox regression model was applied to assess the HR and its 95% CI. This model was not adjusted for any covariates.

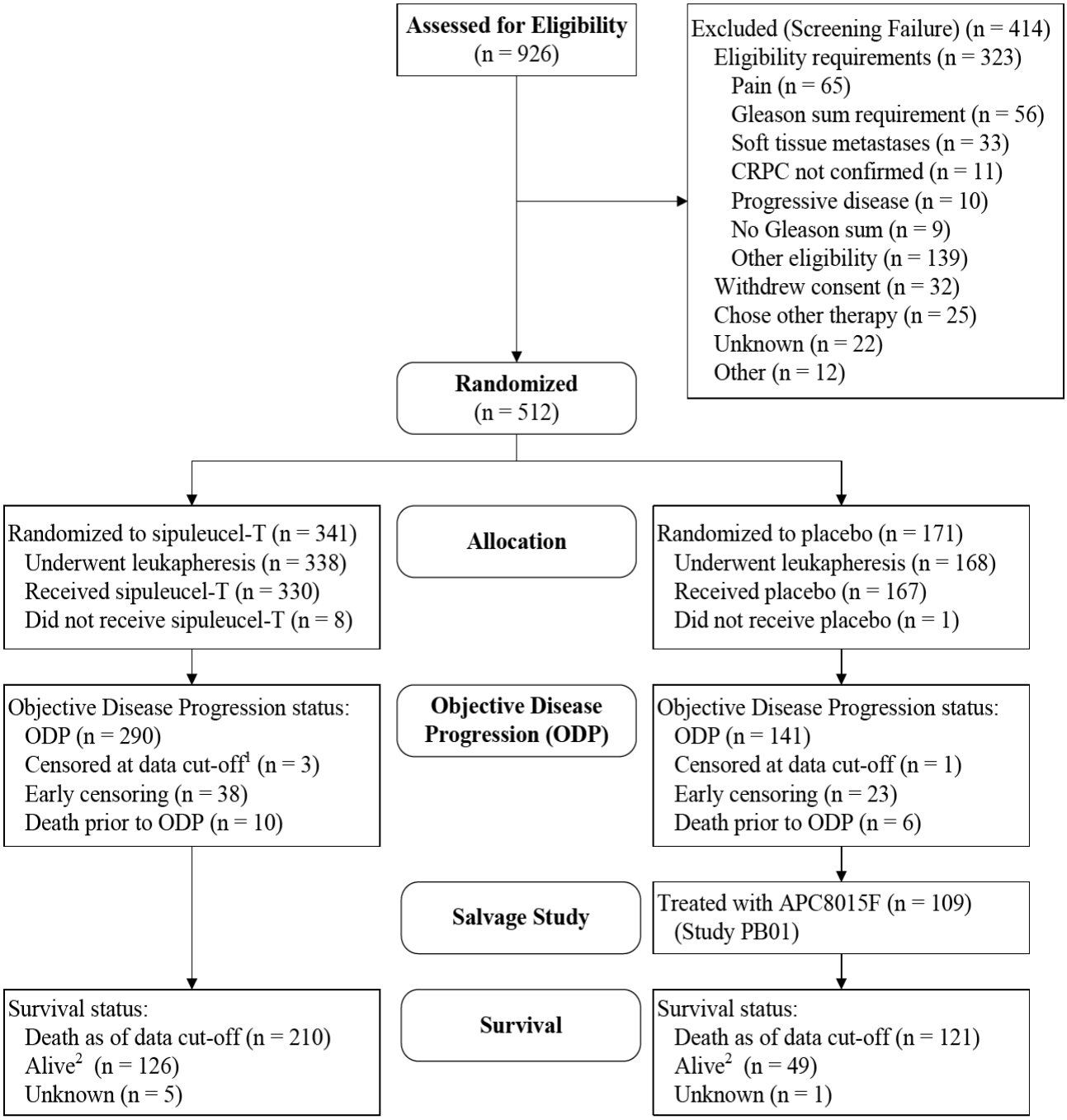
3.1.3 Patient Disposition, Demographic and Baseline Characteristics (Study D9902B)

Of the 926 patients screened for eligibility, 414 patients were screening failures and 512 patients were randomized between August 29, 2003 and November 9, 2007 across 75 clinical trial sites. Of the patients randomized, 341 were randomized to Sipuleucel-T and 171 were randomized to placebo. The clinical database was locked on April 6, 2009. January 18, 2009 was used as the data cut-off-date for the final analysis.

506 patients underwent at least 1 leukapheresis procedure, and 497 patients received at least 1 infusion. A patient disposition schema, including reasons for screening failure, is presented in Figure 1. Major eligibility deviations occurred for 2.0% of patients (6 patients randomized to Sipuleucel-T and 4 patients randomized to placebo as shown in Table 2). No patient received a treatment different from the randomized treatment.

Patient demographics, baseline characteristics, and other baseline values appeared similar between treatment groups. Summaries of demographics and baseline characteristics are presented in Table 3.

Figure 1 Patient Disposition



[1] The data cut-off date was 18 JAN 2009.
[2] Last contact occurred after beginning of survival sweep (12 JAN 2009).

Table 2 Major Protocol Eligibility Deviations

Subject Number	Treatment Group	Protocol Amendment	Deviation Type	Description
92024-0376	Sipuleucel-T	6	Exclusion Criteria	Subject has lung, liver, or known brain metastases, pleural effusions or ascites.
92025-0686	Sipuleucel-T	6	Inclusion Criteria	Subject has adequate hematologic, renal and liver functions as required by the protocol.
92026-0641	Sipuleucel-T	6	Exclusion Criteria	Subject has symptomatic metastatic disease, as defined in the protocol.
92048-0246	Sipuleucel-T	5	Exclusion Criteria	Subject has symptomatic metastatic disease, as defined in the protocol.
92056-0866	Sipuleucel-T	7	Exclusion Criteria	Subject has a history of stage III or greater cancer, excluding prostate cancer, or has been inadequately treated for Stage I or II cancer and has not been disease-free ≥ 3 years prior to registration.
92108-0549	Sipuleucel-T	6	Inclusion Criteria	Subject has current or historic evidence of androgen independent prostatic adenocarcinoma, as defined in the protocol.
92074-0311	Placebo	5	Exclusion Criteria	Subject has symptomatic metastatic disease, as defined in the protocol.
92102-0535	Placebo	6	Exclusion Criteria	Subject has symptomatic metastatic disease, as defined in the protocol.
92136-1228	Placebo	7	Inclusion Criteria	Subject is medically or surgically castrated and serum testosterone is < 50 ng/dL, as defined in the protocol.
92153-0746	Placebo	7	Exclusion Criteria	Subject has moderate or severe symptomatic metastatic disease, as defined in the protocol.

Table 3 Summary of Patient Demographics and Baseline Characteristics

Patient Characteristic	PROVENGE® (N = 341)	Placebo (N = 171)
Age (yrs)		
Median (min, max)	72 (49, 91)	70 (40, 89)
Race (%)		
Caucasian	89.4	91.2
African American	6.7	4.1
Asian, Hispanic, or Other	3.8	4.7
ECOG Performance Status (%)		
0	82.1	81.3
Gleason Sum (%)		
≤ 7	75.4	75.4
Weight		
Median lbs (min, max)	194 (116, 384)	190 (132, 300)
Median kgs (min, max)	88 (53, 175)	86 (60, 136)
Time from Diagnosis to Randomization (yrs)		
Median (min, max)	7.1 (0.8, 24.5)	7.1 (0.9, 21.5)

Patient Characteristic	PROVENGE® (N = 341)	Placebo (N = 171)
Disease Localization (%)		
Bone only	50.7	43.3
Soft tissue only	7.0	8.2
Bone and soft tissue	41.9	48.5
Laboratory Values		
Serum PSA, median ng/mL	51.7	47.2
Serum PAP, median U/L	2.7	3.2
Alkaline phosphatase, median U/L	99.0	109.0
LDH, median U/L	194.0	193.0
Hemoglobin, median g/dL	12.9	12.7
White blood cell count, median x $10^3/\mu L$	6.2	6.0
Total absolute neutrophil count, median x $10^3/\mu L$	4.0	4.1
Stratification Factors, n (%)		
Primary Gleason Grade		
≤ 3	144 (42.2)	71 (41.5)
≥ 4	197 (57.8)	100 (58.5)
Bone Metastases		
0 – 5	146 (42.8)	73 (42.7)
6 – 10	49 (14.4)	25 (14.6)
> 10	146 (42.8)	73 (42.7)
Bisphosphonate Use		
Yes	164 (48.1)	82 (48.0)
No	177 (51.9)	89 (52.0)
Prior Prostate Cancer Therapy, n (%)		
Hormone therapy received	341 (100.0)	171 (100.0)
Combined androgen blockade	279 (81.8)	141 (82.5)
Orchiectomy	32 (9.4)	13 (7.6)
Chemotherapy	67 (19.6)	26 (15.2)
Docetaxel	53 (15.5)	21 (12.3)
Radical prostatectomy	121 (35.5)	59 (34.5)
Radiotherapy (to the prostate bed)	185 (54.3)	91 (53.2)

Abbreviations: ECOG = Eastern Cooperative Oncology Group

3.1.4 Results and Conclusions (Study D9902B)

3.1.4.1 Overall Survival Analysis (Study D9902B)

I. Final Analyses

At the time of the final primary analysis, there were 61.6% death events (210/341) in the Sipuleucel-T arm and 70.8% death events (121/171) in the placebo arm. The observed median survival time for patients randomized to Sipuleucel-T arm was 4.1 months longer than that for patients randomized to placebo (25.8 vs. 21.7 months). The HR was 0.775 [95% CI: 0.614, 0.979]. Detailed results for the final analysis are presented in Table 4, Figure 2, and Table 5. The study achieved a p-value of 0.032 from the analysis using all death events (331) available on the final analysis cut-of-date.

Table 4 Overall Survival Analysis

	Sipuleucel-T (N = 341)	**Placebo (N = 171)**
Censored, n (%)	131 (38.4)	50 (29.2)
Censored prior to survival sweep[1], n (%)	5 (1.5)	1 (0.6)
Events, n (%)	210 (61.6)	121 (70.8)
Median Survival Time (Months; 95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)
Median Follow-Up Time (Months)		
Observed	20.6	19.3
Estimated[2]	33.7	35.9
Primary Model[3]		
p-value	0.032	
Hazard Ratio (95% CI)	0.775 (0.614, 0.979)	
Unadjusted Analysis[4]		
p-value	0.023	
Hazard Ratio (95% CI)	0.766 (0.608, 0.965)	

[1] Censored prior to the beginning of the survival sweep. Only 4 of these patients had less than 6 months of follow-up (3 patients randomized to Sipuleucel-T and 1 patient randomized to placebo).
[2] From the reverse Kaplan-Meier method treating death event as censored.
[3] From a Cox regression model with treatment, PSA (ln), and LDH (ln) as the independent variables, stratified by randomization strata.
[4] p-value was obtained from log-rank test and HR was obtained from a Cox regression model with treatment as the independent variable, both stratified by randomization strata.

Figure 2 Overall Survival Curves, ITT Population

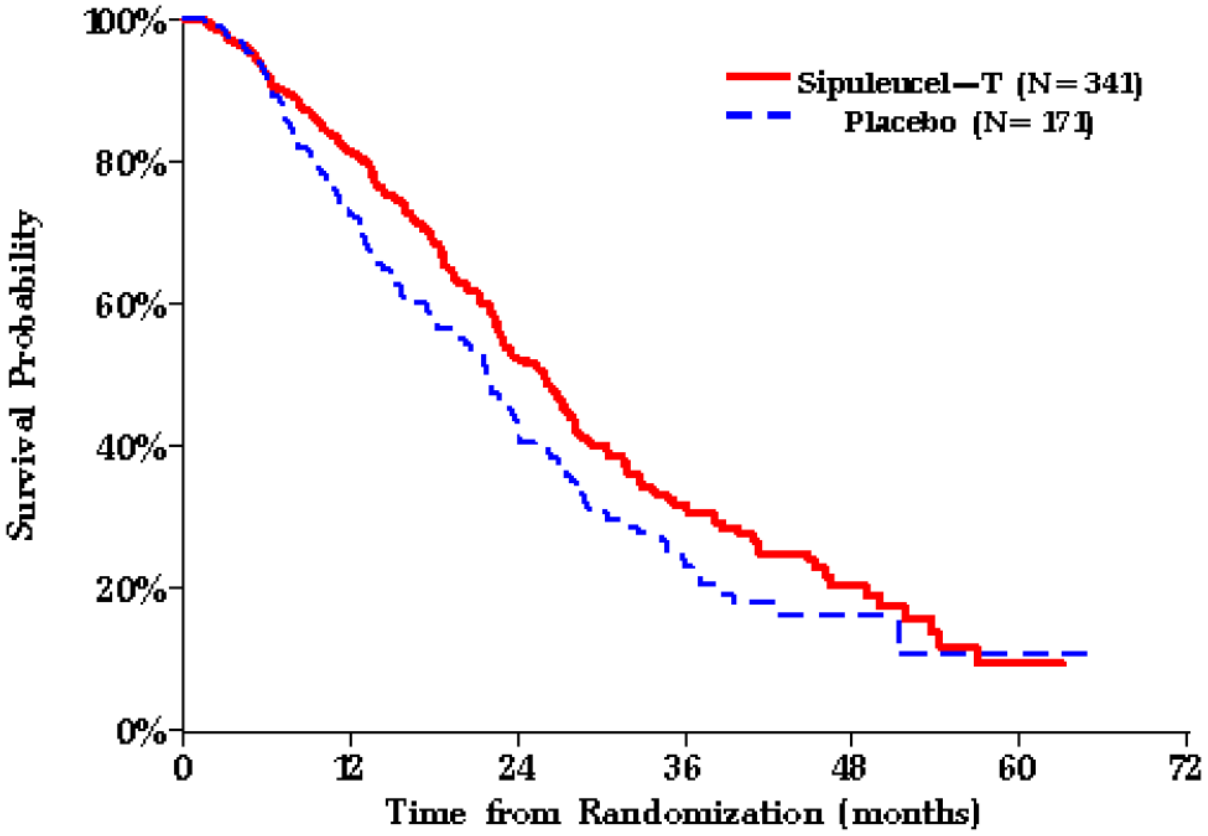


Table 5 Analysis of Overall Survival, Kaplan-Meier Survival Rate Estimates

Treatment	12 Months	24 Months	36 Months	48 Months
Sipuleucel-T	81.1	52.1	31.7	20.5
Placebo	72.4	41.2	23.0	16.0

Because the target number of events specified in the protocol was 304, a supplemental analysis using the first 304 death events was conducted. The cut-off date for the analysis is 11/3/2008 when the first 304 events occurred. The same model that was applied to the primary analysis was used for this analysis. The results of this analysis (p = 0.035, HR = 0.770 [95% CI: 0.605, 0.982]) were consistent with the results observed in the final survival analysis of 331 death events.

The reviewer has duplicated all the above survival analyses and found that the results are consistent with those the sponsor presented. Five patients (two in the Sipuleucel-T arm and three in placebo arm) died after the cut-off date for the final analysis and their dates of death were recorded in the "DEATH" database, but they were censored on the cut-off-date for the final analysis. The reviewer also conducted the survival analysis using the same statistical method as pre-specified for the primary analysis for all death events (336). A p-value of 0.0231 is obtained

which is consistent with the other two analyses using the death events of 304 and 331, respectively.

II. Sensitivity Analyses

Sensitivity analyses were performed to test the robustness of the survival results. Such analyses were performed to determine whether some aspect of the study conduct or the data may have influenced the results observed for survival.

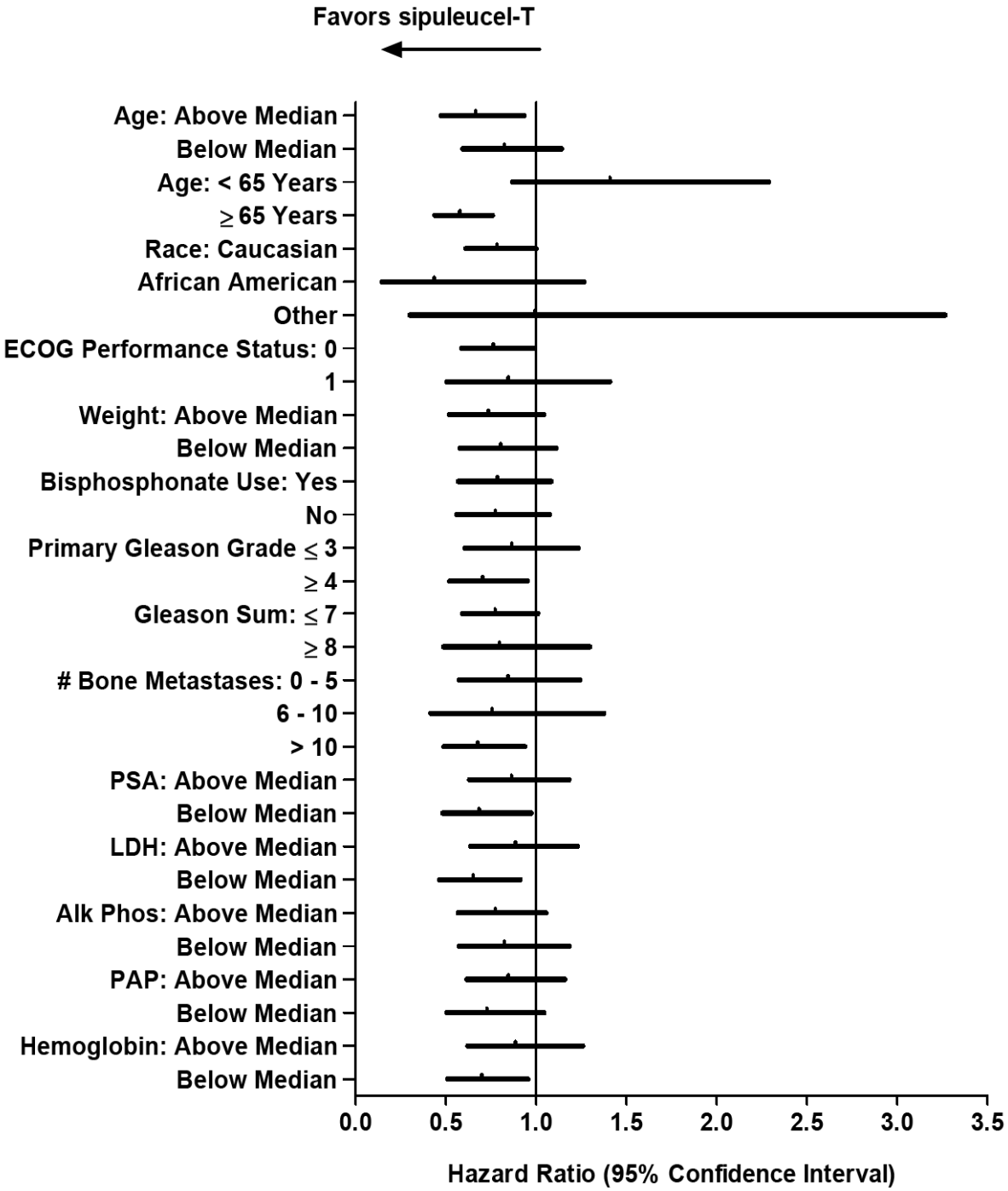
- Overall survival without imputing missing baseline covariates (2 patients had their baseline LDH values imputed due to missing data)
- Overall survival unadjusted for baseline prognostic factors (including log-rank test)
- Overall survival adjusting for additional baseline prognostic factors
- Overall survival adjusting for each of the 21 baseline factors
- Overall prostate cancer specific survival
- Overall survival using modified efficacy populations

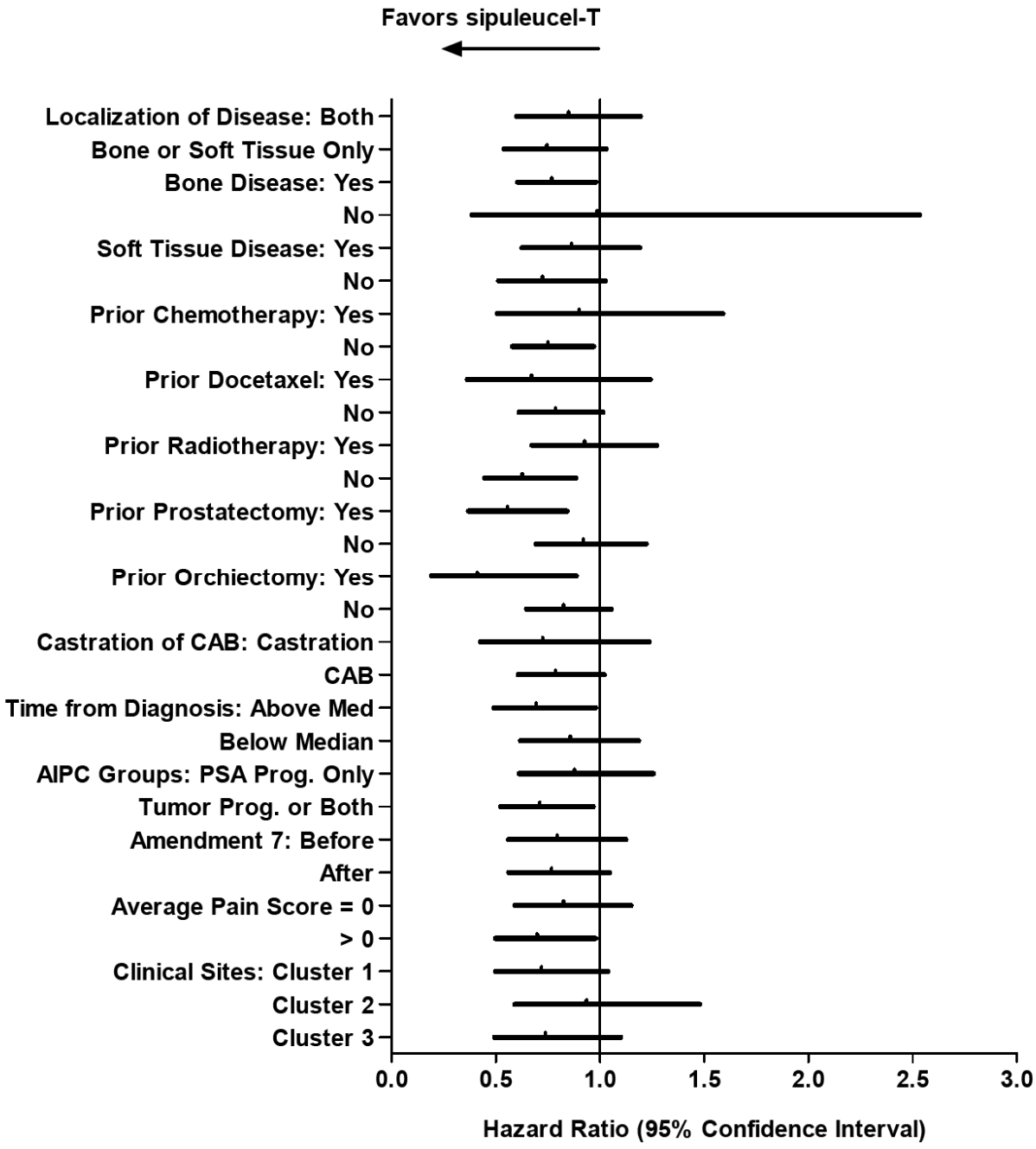
The results of the survival sensitivity analyses are consistent with the results observed in the final analysis of overall survival; in each of the above-mentioned sensitivity analyses, patients randomized to Sipuleucel-T showed an improvement in overall survival compared to those randomized to placebo. The p-values from the sensitivity analyses ranged from 0.009 to 0.052 and most of them were below 0.043, the nominal significance level for the final analysis.

III. Subgroup Analysis

To assess treatment consistency, HRs and corresponding CIs for various patient subgroups were estimated. Key baseline variables were dichotomized with the median used for continuous variables. Forest plots displaying all subgroups based on 27 baseline covariates are shown in Figure 3. Out of the subgroups as defined by 27 baseline covariates, the treatment effect favored Sipuleucel-T T (estimated HR < 1) for almost all subgroups.

Figure 3 Subgroup Analysis





IV. Analysis of Docetaxel Treatment Following Randomization

The D9902B trial design allowed patients to be treated at the physician's discretion with other anti-cancer interventions following objective disease progression. The percentage of patients who received any salvage treatment following study treatment was 81.8% for patients randomized to Sipuleucel-T and 85.4% for patients randomized to placebo. The median time

from randomization to first salvage treatment intervention was 5.4 months (range 0.7 to 49.5 months) in the Sipuleucel-T arm and 4.5 months (range 1.0 to 36.5 months) in the placebo arm. If the treatment of frozen Sipuleucel-T was excluded as the salvage treatment, then the median time for the placebo arm was 6.2 months (range 1.0 to 36.5 months) and the percentage of placebo patients who received any non- frozen Sipuleucel-T salvage treatment was 73.1%.

There were 49.1% (81/171) of the placebo patients who received the frozen Sipuleucel-T treatment as their first anti-cancer intervention and 63.7% (109/171) placebo patients who received frozen Sipuleucel-T at some time. The median time from randomization to first infusion of Sipuleucel-T was 5.7 months (range 2.2 to 31.1 months).

The only treatment in metastatic castration resistant prostate cancer (may be considered equivalent to AIPC) with a known survival benefit is docetaxel. Study TAX 327 was conducted under a CDER IND, in which the median survival advantage was 2.4 months (18.9 vs. 16.5 months for docetaxel + prednisone vs. mitoxantrone + prednisone,). It is noted that the characteristics of the population at study entry between D9902B and TAX 327 are different. TAX 327 enrolled a more symptomatic population, most of whom required narcotic analgesics, while D9902B enrolled minimally symptomatic patients and excluded patients who required narcotic analgesics. Baseline PSA was 536 in TAX 327 whereas baseline PSAs were 57 and 42 on the experimental and control arms of 9902B, respectively.

Due to the fact that approximately half of the placebo patients received the frozen Sipuleucel-T treatment as their first anti-cancer intervention in Study D9902B, fewer patients in the placebo arm were treated with docetaxel following disease progression, compared to the Sipuleucel-T treated patients. The percentage of patients who were known to have received docetaxel following study treatment was 57.2% for patients randomized to Sipuleucel-T and 50.3% for patients randomized to placebo. Among patients who received docetaxel at any time following randomization, the median time from randomization to post-treatment docetaxel use was 7.2 months (range 1.3 to 49.5 months) in the Sipuleucel-T arm and 9.6 months (range 1.0 to 36.5 months) in the placebo arm. Therefore, there is a concern that the survival difference between the two arms may be attributable to the post-treatment of docetaxel.

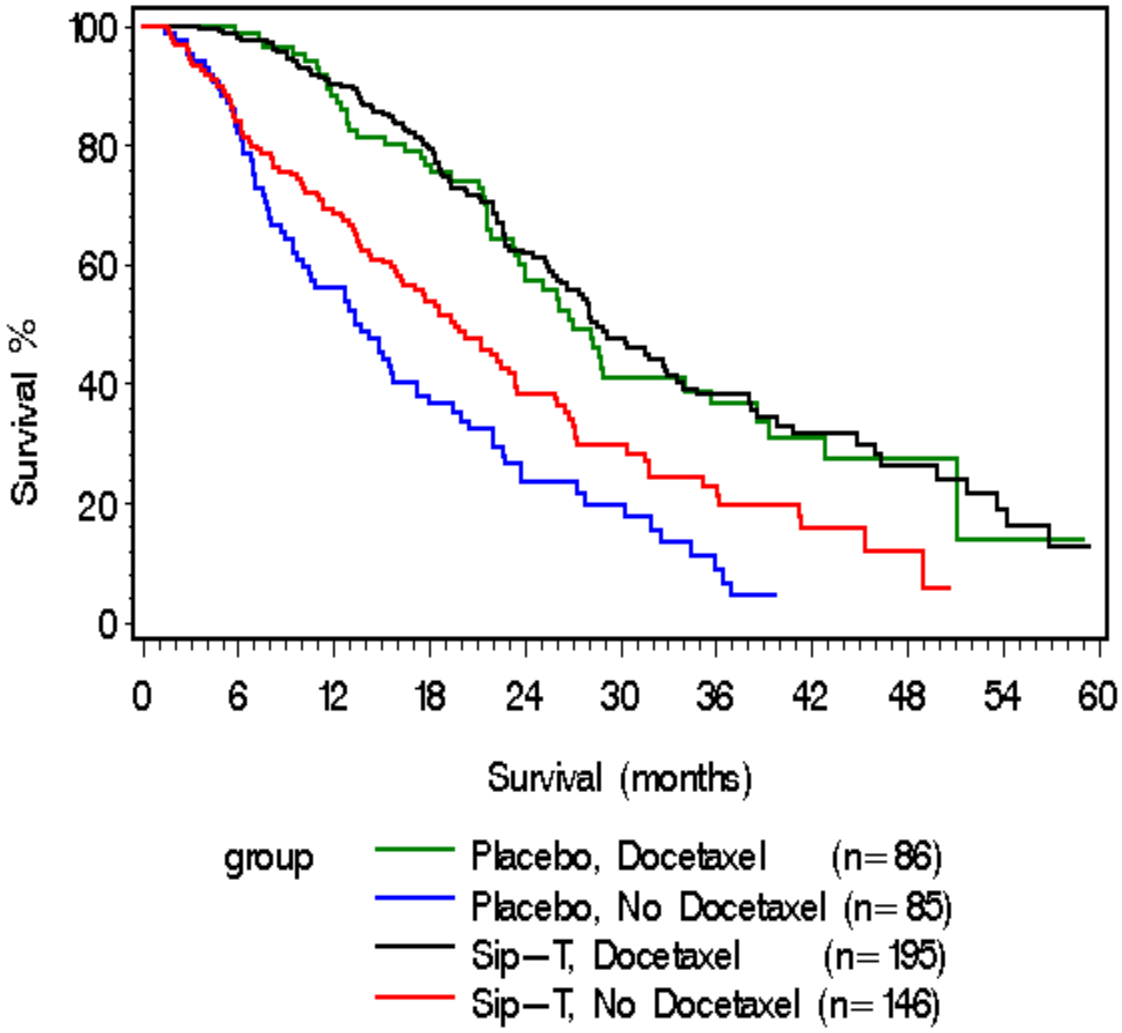
This reviewer conducted a number of independent sensitivity analyses to see if the post-treatment of docetaxel has any impact on survival. The analyses were conducted before looking at the sponsor's results and conclusion for this issue. For the following analyses, the reviewer also consulted with the Special Government Employee (SGE). The SGE supported the analyses and suggested also providing descriptive statistics by stratifying time to salvage therapy.

The first analysis below presents the possible hypothetical explanations for the observed outcomes with respect to Sipuleucel-T survival benefit by the two subgroups. The second analysis shows the additional analysis results from two different Cox models. The third analysis is used to support the results from the time dependent Cox model in the second analysis as suggested by the SGE. The last analysis describes the baseline characteristics between the two arms by the two subgroups. Due to the nature of the post-hoc analyses, cautions should be used in interpreting the results, especially the p-values.

1. **Analysis of overall survival by docetaxel subgroups**

Figure 4 displays the results for the overall survival analyses by two docetaxel subgroups (use of docetaxel or not). Since the use of post-study docetaxel treatment or not is likely to be an outcome-driven-event and is not randomized, patients between Sipuleucel-T treated and placebo arms in each of the two subgroups might not be comparable.

Figure 4 Survival Analysis by Docetaxel Subgroup



For the comparisons in a non-randomized setting one can adjust for the known baseline characteristics with an appropriate model (the reviewer did the analyses and did not find anything substantially different from the results presented in this section), but can not adjust for the unmeasured characteristics. To explore whether the observed results in figure 4 might be due to an imbalance in unmeasured characteristics, three possible assumptions regarding the comparability of the two treatment arms within each subgroup are presented based on the fact that the overall two treatment arms were randomized and the observation that the two arms were reasonably comparable.

Assumption 1- More patients with good prognosis were in the placebo arm, compared to the Sipuleucel-T arm in the subgroup receiving docetaxel. It also implies that more patients with poor prognosis were in the placebo arm in the other subgroup in which patients who did NOT receive docetaxel since the overall two treatment arms were comparable.

In the subgroup receiving docetaxel (black and green lines in figure 4), the median time from randomization to first docetaxel in the placebo arm was 2.4 months longer than that in Sipuleucel-T arm, which implies that placebo needed to live longer on average to receive docetaxel, and further indicates that more good prognostic patients were in the placebo arm, compared to the Sipuleucel-T arm in that subgroup. One hypothetical scenario might be that placebo patients should live on average at least 2.4 months longer than patients in Sipuleucel-T arm due to the selection bias in the post-hoc docetaxel subgroup. The observed median survival difference was 1.4 months between the two arms as presented in Table 6 ("Docetaxel therapy" row). If one takes the 2.4 months delayed docetaxel treatment into account, the survival benefit might be 3.8 (2.4+1.4) months between the two arms in the post-hoc docetaxel subgroup. However, this is just hypothetical, based on post-hoc analysis in non-randomized subgroups.

On the other hand under the same assumption, the median survival difference of 6 months between the placebo and Sipuleucel-T arms (blue and red lines in figure 4) in the post-hoc subgroup that did not use docetaxel would be smaller if the placebo and Sipuleucel-T patients in this post-hoc subgroup were comparable. Again, this is just another hypothesis.

Table 6 Survival Analysis by Docetaxel Subgroup

	Sipuleucel-T		Placebo		Sipuleucel-T vs. placebo	
	N	Median Survival[1]	N	Median Survival[1]	Hazard Ratio (95% CI)[2]	p-value[2]
Docetaxel Therapy	195	28.5	86	27.1	0.935 (0.669, 1.307)	0.694
No Docetaxel Therapy	146	19.6	85	13.6	0.677 (0.498, 0.918)	0.012

[1] Based on a Kaplan-Meier estimate (in months).
[2] HR and p-value estimated based on Cox model with treatment as independent variable.

Assumption 2- The two treatment arms were comparable in both subgroups.

This assumption implies that there was an interaction between Sipuleucel-T and docetaxel, and Sipuleucel-T could work for patients who did not receive docetaxel, but had minimal or no effect for patients who received subsequent therapy with docetaxel.

Assumption 3- More patients with good prognosis were in the Sipuleucel-T arm, compared to the placebo arm in the subgroup receiving docetaxel. It also implies that

more patients with poor prognosis were in the Sipuleucel-T arm in the other subgroup in which patients who did NOT receive docetaxel.

If this assumption were true, it would clearly indicate an interaction between Sipuleucel-T and docetaxel arms, and Sipuleucel-T could only work for patients who did not receive docetaxel, but had no effect or might be harmful for patients who received subsequent therapy with docetaxel.

Based on the fact that the overall two treatment arms were randomized and the observation that the two arms were reasonably comparable, the three above assumptions should be the only ones that can be made. Under Assumption 1, it is likely that Sipuleucel-T had improvement in overall survival for both subgroups as discussed in the previous paragraphs. The two other assumptions imply that there was an interaction between Sipuleucel-T and docetaxel, and Sipuleucel-T could only work for the patients who did not receive docetaxel. Therefore, whether Sipuleucel-T had improvement in overall survival for the whole patient population or for only one subgroup depends on which of the three assumptions is true.

However, the second and the third assumptions are unlikely to be true and the first assumption is very likely to be true. This was based on the fact that the placebo patients received docetaxel in the later time, and thus needed to liver longer before they had a chance to be treated with docetaxel.

Based on the above analyses, the reviewer concludes that overall treatment effect of Sipuleucel-T seen in Figure 2 was not altered by the subsequent-treatment of docetaxel.

It should be emphasized that the groups represented by the lines in figure 4 do not represent the groups to which treatments were randomly allocated. These post-hoc analyses should be only used to see whether the overall conclusion of survival benefit for Sipuleucel-T treatment seen in Figure 2 is altered by the subsequent-treatment of docetaxel or not. Because of the groups represented by the lines in figure 4 were not randomly allocated, one can not use Figure 4 to conclude that there was no Sipuleucel-T treatment benefit in patients treated with subsequent docetaxel. It is not possible to determine the precise effect of docetaxel on survival given the design of this clinical trial and the data available in the submission.

2. **Analysis of overall survival by the two different models**

Since it is impossible to know what would have happened to these patients if they had not received docetaxel, the docetaxel effect was re-assessed by censoring patients at time of docetaxel initiation with the same Cox model used for the primary analysis. In addition, the same Cox model for the primary analysis was used again by treating docetaxel as a time-dependent covariate. The results from the two models together with results from the primary analysis as reference are presented in Table 7 to support the conclusion drawn in the first analysis. The sponsor also did the same analyses and their results are consistent with those in Table 7.

Table 7 Sensitivity Analysis in Cox Model

	Sipuleucel-T vs. placebo Hazard Ratio (95% CI)		p-value
The primary analysis	0.775	(0.614, 0.979)	0.032
Censoring patients at time of docetaxel initiation	0.649	(0.469, 0.898)	0.009
Time-dependent covariate for docetaxel use	0.777	(0.615, 0.981)	0.034

3. **Analysis of overall survival by time to receive docetaxel**

As suggested by the SGE, this analysis provides descriptive statistics by stratifying time to salvage therapy to further support the results from the time dependent Cox model since it is equivalent to considering time to salvage therapy as a time dependent covariate in the Cox model. Medians times to receive docetaxel are 7.2, 7.9, and 9.6 months for the Sipuleucel-T arm, all patients who received docetaxel, and the placebo arm, respectively. The survival analyses were conducted by the subgroups using these three medians as the cut-of-time, as well as using the four quartiles from all patients who received docetaxel. Since sample size is relatively small in the subgroup analysis, the Cox model with only treatment as independent variable was used to estimate HR and p-value. As shown in Table 8, the median survival in the Sipuleucel-T arm is numerically better than that in the placebo arm in all subgroups except the one that patients received docetaxel in Q1. However, there were only 15 patients in the placebo arm.

Table 8 Analysis of Overall Survival by Time To Receive Docetaxel

Docetaxel Timing (in Mons)	Sipuleucel-T N	Sipuleucel-T Median Survival[1]	Placebo N	Placebo Median Survival[1]	Sipuleucel-T vs. placebo Hazard Ratio (95% CI)[2]	p-value[2]
All	195	28.5	86	27.1	0.935 (0.669, 1.307)	0.694
≤ 7.2	97	22.3	32	21.1	0.865 (0.538, 1.390)	0.549
> 7.2	98	44.8	54	35.6	0.768 (0.473, 1.244)	0.283
≤ 7.9	106	22.3	35	21.1	0.808 (0.515, 1.268)	0.353
> 7.9	89	44.8	51	35.6	0.795 (0.477, 1.325)	0.378
≤ 9.6	123	23.1	43	21.5	0.861 (0.568, 1.304)	0.480
> 9.6	72	46.4	43	38.6	0.721 (0.403, 1.290)	0.270
Q1[3]	55	19.2	15	19.9	1.155 (0.577, 2.313)	0.685
Q2	51	25.6	20	21.3	0.563 (0.306, 1.036)	0.065
Q3	43	28.9	26	25.1	0.652 (0.345, 1.235)	0.190
Q4	46	53.7	25	51.2	1.156 (0.475, 2.811)	0.750

[1] Based on a Kaplan-Meier estimate (in months).
[2] HR and p-value estimated based on Cox model with treatment as independent variable.
[3] time to receiving docetaxel were broken into four quartile groups: Q1: ≤ 4.5, Q2: >4.5 — ≤7.86, Q3: >7.86 — ≤ 13.38, Q4: > 13.38 months.

4. **Summary of baseline factors by docetaxel subgroup**

As shown in Table 9 for patients who received subsequent docetaxel treatment following randomization, more patients were observed in the placebo arm in terms of *ECOG status* (0) and *bone and soft tissue*, compared to the Sipuleucel-T arm. Placebo patients also had longer median *time from diagnosis to randomization* and higher median *serum PAP*. However, in terms of *primary Gleason grade* ≤ 3, >10 *bone metastases*, *prior chemotherapy*, and *prior docetaxel*, more patients were observed in the Sipuleucel-T arm, compared to the placebo arm. Sipuleucel-T treated patients also had higher median *serum PSA*.

At a minimum, the results do not support that the known baseline characteristics in the Sipuleucel-T treated arm are better than the placebos in the docetaxel treated subgroup, but the fact that placebo treated patients received docetaxel much later indicates that placebo patients needed to be alive longer than the Sipuleucel-T treated patients to receive docetaxel so they are likely to be better than the Sipuleucel-T treated patients in terms of unknown characteristics.

Table 9 Summary of Baseline Factors by the Use of Docetaxel

	Docetaxel		No Docetaxel	
	Sipuleucel-T (N=195)	Placebo (N=86)	Sipuleucel-T (N=146)	Placebo (N=85)
Age, median years (min, max)	70 (49, 88)	69 (53, 87)	74 (49, 91)	73 (40, 89)
Race, Caucasian (%)	89.7	91.9	89.0	90.6
ECOG status, 0 (%)	82.6	86.1	81.5	76.5
Gleason sum ≤ 7, (%)	75.4	73.3	75.3	77.7
Weight, median kgs (min, max)	90 (66, 159)	88 (65, 128)	86 (53, 175)	85 (60, 136)
Time from diag. to randomization, median years (min, max)	6.7 (0.8, 22,6)	7.4 (1.0, 16.6)	7.7 (0.8, 24,5)	6.5 (0.9, 21.5)
Disease localization, (%)				
Bone only	48.5	39.5	54.1	47.1
Soft tissue only	7.2	8.2	6.9	8.2
Bone and soft tissue	44.3	52.3	39.0	44.7
Primary Gleason Grade ≤ 3, (%)	43.1	38.4	41.1	44.7
Bone Metastases, (%)				
0 – 5	46.2	44.2	38.3	41.2
6 – 10	13.8	18.6	15.1	10.6
> 10	40.0	37.2	46.6	48.2
Bisphosphonate Use, (%)	49.7	51.2	45.9	44.7
Serum PSA, median ng/mL(min, max)	50 (5, 8005)	36 (6, 3745)	61 (5, 2370)	55 (7, 1519)
Serum PAP, median U/L (min, max)	2.6 (0.6, 466)	3.4 (0.6, 93)	2.8 (0.6, 433)	2.8 (0.6, 147)
Alkaline phosphatase, median U/L	96 (38, 2031)	104 (46, 607)	103 (18, 2396)	120 (43, 2813)
LDH, median U/L (min, max)	193 (115, 598)	194 (101, 654)	196 (84, 637)	192 (131, 1662)
Hemoglobin, median g/dL (min, max)	13 (8, 18)	13 (9, 15)	13 (9, 16)	13 (9, 15)
Prior Orchiectomy, (%)	8.2	5.8	11.0	9.4
Prior Chemotherapy, (%)	11.3	9.3	30.8	21.2
Prior Docetaxel, (%)	7.2	4.7	26.7	20.0
Prior Radical prostatectomy, (%)	37.4	34.9	32.9	34.1
Prior Radiotherapy, (%)	53.3	55.8	55.5	50.1

In summary, the above analyses of docetaxel treatment following randomization did not provide evidence that the survival difference between the two arms was attributable to the post-treatment of docetaxel.

V. Additional Analyses

A. Discrepancies

The clinical reviewers raised some concerns about the discrepancies in some data sets during their review and sent them to the sponsor. Although the sponsor has provided additional documents and information to adequately respond these concerns as shown in Amendment 36, the statistical reviewer conducted some sensitivity analyses to further address the concerns as shown below.

1. Discrepancy in date of randomization (DOR) between Investigator's determination in the CRF and dataset used for final analysis

Subject ID	Dataset DOR	Investigator's DOR
92026-0882	07/24/2006	06/30/06
92104-0316	07/12/2004	07/08/04
92503-0914	10/12/2006	10/11/06
92061-0326	07/16/2004	Not provided
92069-1239	09/24/2007	09/19/07
92122-0243	02/20/2004	Not provided
92142-0404	09/27/2004	09/24/04
92168-1199	07/13/2007	07/16/07
92503-0912	09/07/2006	09/06/06
92503-1011	01/25/2007	01/23/07

If repeating the primary analysis using the investigators' dates and excluding the two patients without the dates, p=0.0269.

2. Patients whose exact date of death was not documented in the CRFs

Subject ID	Dataset DOD	Investigator's DOD	DC/SSDI DOD	Comments
92142-0901	--b(6)---	Unk/unk/07	--b(6)---	
92101-1273	--b(6)---	10/unk/08	Not provided	Per wife, exact date unknown
92505-0799	--b(6)---	03/unk/08	Not provided	

Repeating the primary analysis by excluding the above patients resulted in a p-value of 0.0315.

3. Patients who had deaths documented by Social Security Index by the DTHDTCNF column in the 9902B DEATH dataset, but their SSIs were not included in the CRF:

92035-0282, 92048-0414, 92101-0294, 92109-0220, 92123-0919, 92146-0271, 92127-0756.

Repeating the primary analysis by excluding the above patients resulted in a p-value of 0.0345.

4. Patients who had deaths documented by death certificates per the DTHDTCNF column in the 9902B DEATH dataset, but their copies could not be found in the CRF:

   92107-0782, 92503-1000, 92036-1014, 92108-0420.

   Repeating the primary analysis by excluding the above patients resulted in a p-value of 0.0336.

5. Patient who had death documented by obituary per the by the DTHDTCNF 9902B DEATH dataset, but the obituary could not be found in the CRF:

   92146-0858.

   Repeating the primary analysis by excluding the above patients resulted in a p-value of 0.0388.

6. Patients who had the date of death confirmed by the investigator based on an obituary (The obituary has been provided, however no death certificate or SSDI was located in the CRF):

   92026-0724 (Death Certificate is not available), 92040-0479 (Date of death:--b(6)---92040-0497 (Date of death: --b(6)-----), 92153-0949.

   Repeating the primary analysis by excluding the above patients resulted in a p-value of 0.0362.

7. Patients who had a date of death documented by the PI but the FDA reviewer could not find corroborating information:

   92036-0318, 92061-0213, 92061-0217, 92061-0326, 92116-1174, 92125-0556, 92146-0258, 92146-0413, 92146-0858, 92152-0447, 92159-0945, 92503-0679, 92505-0894, 92508-1004.

   Repeating the primary analysis by excluding the above patients resulted in a p-value of 0.0425.

Repeating the primary analysis by excluding ALL patients in the lists from 2-7 resulted in a p-value of 0.0496. None of the above sensitivity analyses alternates the findings from the primary analysis.

B. Major protocol deviations and date of death deviations

1. Ten patients were identified by the sponsor with major protocol deviations as shown in Table 2. Repeating the primary analysis by excluding these 10 patients resulted in a p-value of 0.0476.

2. Three more patients were identified by the clinical reviewer with potential major protocol violations due to the uncertainty of their serum testosterone levels at baseline:

   92048-0364, 92027-0470, 92048-0244.

   Repeating the primary analysis by excluding the above three patients resulted in a p-value of 0.0338. If excluding the above three patients plus the ten with major protocol violations identified by the sponsor and repeating the primary analysis, a p-value of 0.0497 was obtained.

3. The clinical reviewer identified two patients with deviations for their date of death data as shown in the following table. Repeating the primary analysis by replacing the dates of death based on the documents provided for verification in the table below resulted in a p-value of 0.0324, no different from the one based on the primary analysis.

Subject ID	Treatment	Date of death in Dataset	Date of death in the documents provided for verification
92146-0413	Placebo	--b(6)---	--b(6)---
92109-0220	Sipuleucel-T	--b(6)---	--b(6)---

   If excluding ALL the above 13 patients with protocol deviations and using the date of death in the documents provided for verification in the above table, p=0.0499 using the same pre-specified Cox model for the primary analysis.

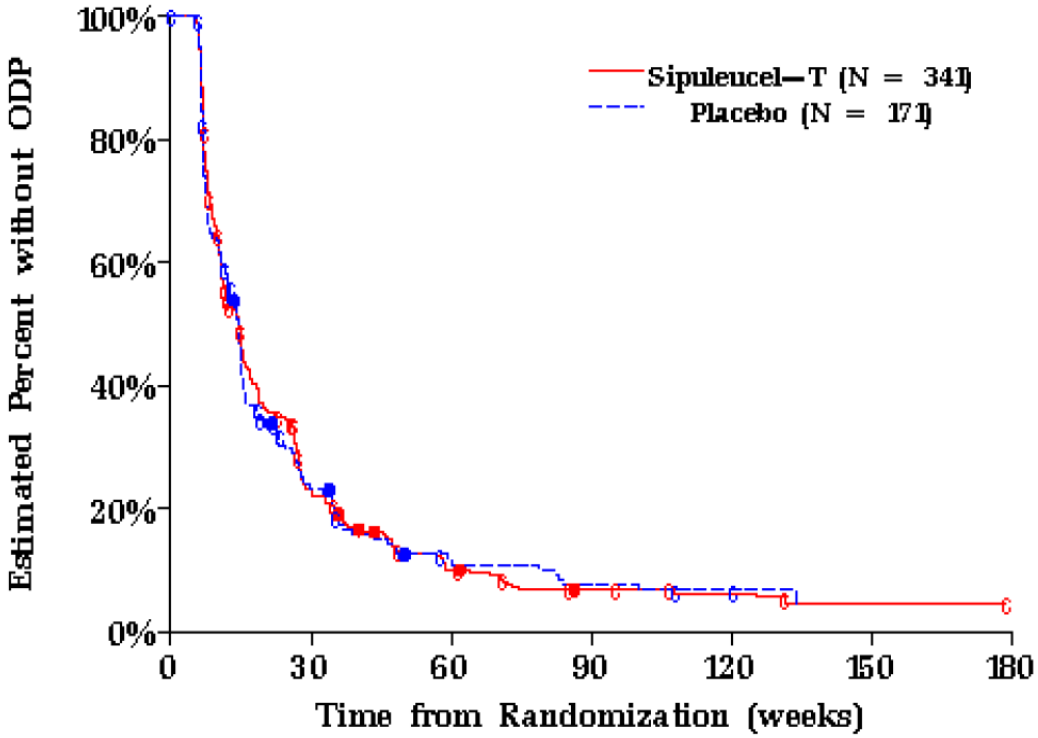
In summary, the results based on the above additional analyses are consistent with those from the primary analysis.

3.1.4.2 Other Endpoints Analysis (Study D9902B)

Time to objective disease progression

No significant delay from randomization to objective disease progression in the Sipuleucel-T arm compared with the placebo arm was observed (HR = 0.951 [95% CI: 0.773, 1.169], p=0.628, Figure 5). The estimated median time to disease progression was 14.6 weeks in the Sipuleucel-T arm compared with 14.4 weeks in the placebo arm.

Figure 5 Time to Objective Disease Progression



Progression free survival

No significant difference in progression free survival was observed in the Sipuleucel-T arm compared with the placebo arm (HR = 0.938 [95% CI: 0.766, 1.149]; p = 0.533, log rank).

Time to clinical progression

No significant difference in time from randomization to clinical progression in the Sipuleucel-T arm compared with the placebo arm was observed (HR = 0.917 [95% CI: 0.749, 1.123]; p = 0.398, log rank).

Time to PSADT

No significant difference in time from randomization to PSADT in the Sipuleucel-T arm compared with the placebo arm was observed.

Immune responses

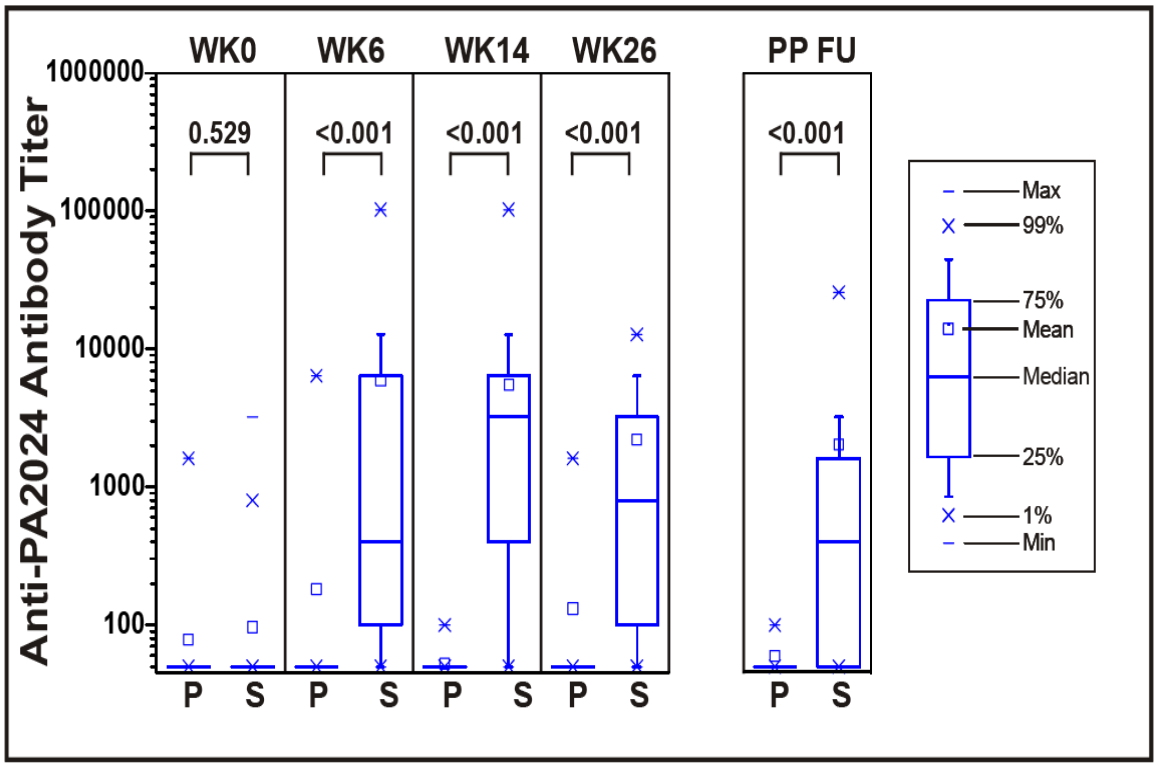
Immune responses were assessed before (Week 0) and after treatment (Weeks 6, 14, and 26, and at the post-progression follow-up visit) in both Sipuleucel-T and placebo patients. Due to sample availability issues, not all patients could be evaluated for immune responses. Prior to Protocol

Amendment 7, immune response samples were only collected from patients at clinical trial sites in close proximity to the --b(4)--- Cell Processing Center. A total of 237 patients treated with either Sipuleucel-T (n = 160) or placebo (n = 77) were evaluated for some of the immune response.

1. Serum Antibody Responses

The serum antibody titer of the PA2024-specific response is presented in Figure 6. The key findings were that only the Sipuleucel-T treated group exhibited immunogen-specific responses post-treatment, and that the responses persisted in the Sipuleucel-T group, implying immunological durability, or memory. The findings are consistent with antibody titers of PAP-, GM-CSF- specific antibody titers.

Figure 6 Anti-PA2024 Antibody Titers in the Placebo (P) and Sipuleucel-T (S) Groups



2. Anti-GM-CSF Neutralizing Antibody Responses

A total of 60 patients were evaluated for GM-CSF neutralizing antibody responses. Ten patients in the Sipuleucel-T group exhibited anti-GM-CSF antibody titers (9 patients at Week 6, 3 patients at Week 14, and 1 patient at Week 26), and 1 patient in the placebo group exhibited an anti-GM-CSF antibody titer at Week 14. One patient in the Sipuleucel-T group exhibited neutralizing activity at all time points evaluated.

3. Cellular IFNγELISPOT Responses

PA2024-specific IFNγELISPOT responses were observed only in the Sipuleucel-T group after treatment. However, little evidence of PAP-specific responses was seen in the Sipuleucel-T group.

4. Cellular Proliferative Responses

Only patients treated with Sipuleucel-T displayed appreciable PA2024-specific proliferative T cell responses post-treatment. PAP-specific proliferative responses were also observed in the Sipuleucel-T group post-treatment, but the response magnitudes were lower than the PA2024-specific proliferative responses.

3.1.4.3 Conclusions (Study D9902B)

In the study of 512 patients with metastatic AIPC, treatment with Sipuleucel-T resulted in a statistically significant improvement in overall survival compared to a placebo control in the primary analysis. The finding was supported by a variety of sensitivity analyses. The only FDA-approved therapy demonstrated to prolong overall survival for men with metastatic AIPC is the chemotherapeutic agent docetaxel. In Study D9902B, more patients in the Sipuleucel-T arm received docetaxel following study treatment, as compared to the placebo. Among patients who received docetaxel at any time following randomization, the median time from randomization to post-treatment docetaxel use in the Sipuleucel-T arm was shorter than that in the placebo arm. However, additional analyses did not show that the survival difference between the two arms was attributable to the post-treatment of docetaxel.

3.1.5 Results from Other Randomized Studies (Studies D9901 and D9902A)

Study D9901 was a Phase 3, randomized, double blind, placebo-controlled, multicenter trial in patients with asymptomatic metastatic castrate resistant prostate cancer. A total of 127 patients were randomized 2:1 to receive Sipuleucel-T (n = 82) or placebo (n = 45).

The primary endpoint of this study was time to disease progression defined as progressive disease on serial radiographic imaging tests, new cancer-related pain associated with a radiographic anatomical correlation, or other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture. PSA was not used as a measure of progression in this study. Overall survival was not a study endpoint.

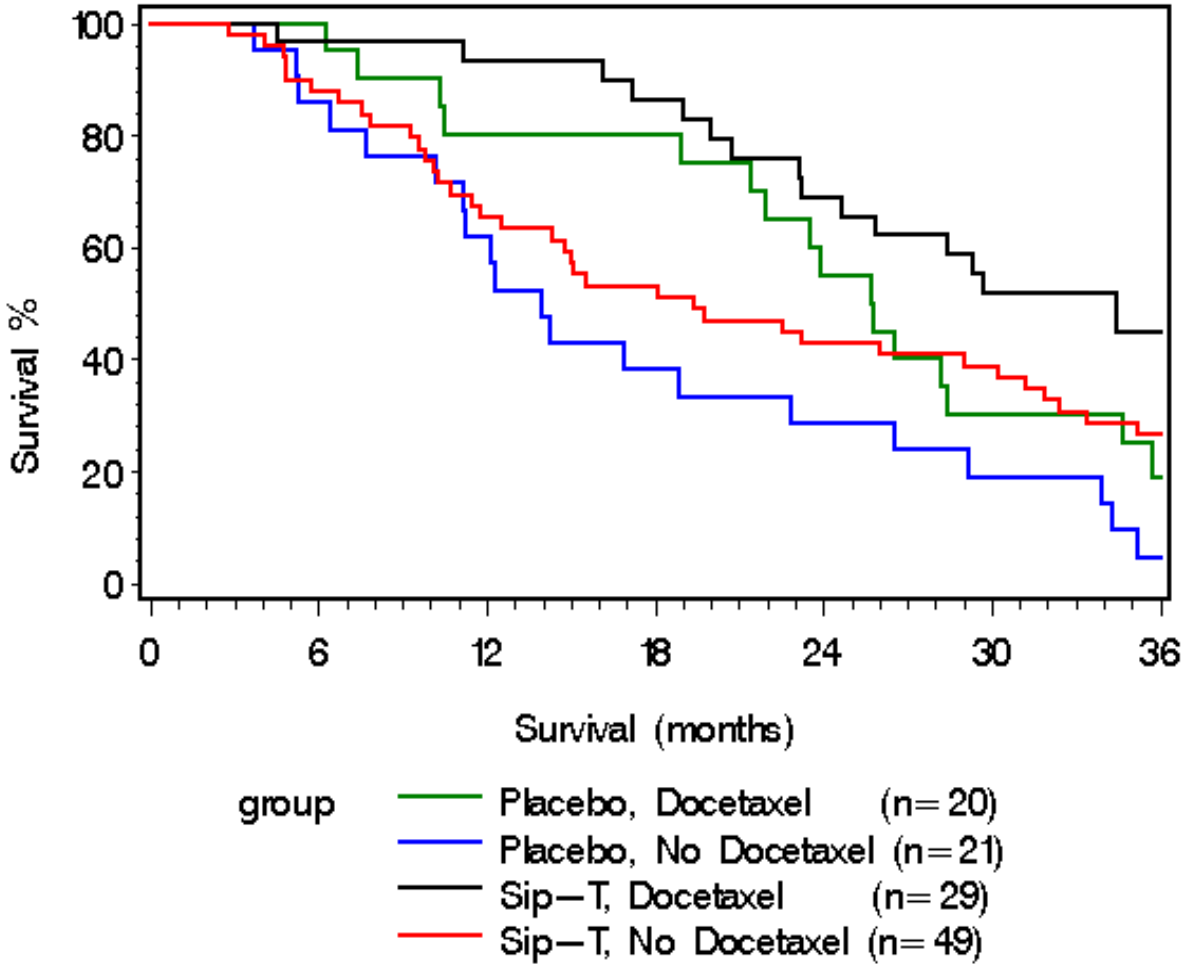
Study D9902A randomized 98 patients in 2:1 ratio to receive Sipuleucel-T (n=65) or placebo (n=33). Study D9902A was identical in design to Study D9901.

Both studies did not meet their primary endpoint and other pre-specified endpoints. However, In Study D9901 with 127 patients, the median overall survival in patients treated with Sipuleucel-T was 25.9 months [95% CI: 20.0, 32.4], compared to 21.4 months [95% CI: 12.3, 25.8] among placebo patients. The log-rank test on the difference between the two arms in overall survival

resulted in a p-value of 0.01. Study D9902A, an identically designed study with 98 patients, only showed a trend toward improvement in overall survival. The median overall survival in patients treated with Sipuleucel-T was 19.0 months [95% CI: 13.6, 31.9], compared to 15.7 months [95% CI: 12.8, 25.4] among placebo patients. It should be noted that overall survival as an endpoint was not defined in both study protocols and the statistical analysis for comparing the two arms in overall survival was not pre-specified.

Based on the available data in Study D9901, 37.2% of Sipuleucel-T treated patients (29/78) and 48.8% of placebo treated patients (20/41) received docetaxel. Because of the higher percentage of placebo treated patients who received docetaxel, the impact of docetaxel treatment following disease progression on survival should be in direction against the claim of Sipuleucel-T benefit if there is a docetaxel treatment benefit. As shown in Figure 7, there exist differences in overall survival between the two arms regardless of docetaxel use or not.

Figure 7 Survival Analysis by Docetaxel Subgroup for Study D9901



Key efficacy results for both studies presented in Section 4.1 of this review memo. Detailed review for these two studies is attached as an appendix to this memo.

3.2 Evaluation of Safety

Sipuleucel-T is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMCs), including APCs, that have been activated ex vivo with a recombinant fusion protein.

The safety evaluation of Sipuleucel-T is primarily based on 601 prostate cancer patients who received Sipuleucel-T in randomized Phase 3 controlled clinical trials. The most common adverse reactions observed in Sipuleucel-T patients at a rate ≥ 5% and at least twice the control arm rate, were chills, pyrexia (fever), headache, myalgia, influenza like illness, and hyperhidrosis (sweating). The majority of adverse reactions were mild or moderate in severity.

Serious adverse events observed in patients treated with Sipuleucel-T include acute infusion reactions, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare. In controlled clinical trials of Sipuleucel-T, cerebrovascular events (hemorrhagic, ischemic, or bleeding from dural metastatic lesions) were observed in 3.5% of patients (21/601) in the Sipuleucel-T arm compared with 2.6% of patients (8/303) in the placebo arm. The difference in cerebrovascular event rate between the two arms could be due to the fact that patients were older in the in Sipuleucel-T arm and patients treated with Sipuleucel-T lived longer or simply due to random variation. Whether there is a causal relationship of cerebrovascular events to Sipuleucel-T remains unclear.

The known risks of treatment with Sipuleucel-T include treatment-related AEs and the risk of non-infusion. The AEs more commonly observed in the Sipuleucel-T arm included chills, pyrexia, headache, influenza like illness, myalgia, hypertension, hyperhidrosis, and groin pain. These events generally appeared to be infusion-related, occurring within 24 hours of an infusion and typically resolved within 2 days or less. The majority of these events was non-serious and was ≤ Grade 2. These types of events were not unexpected, and appeared to be consistent with cytokine release - an expected consequence of Sipuleucel-T's immunological mechanism of action.

Sipuleucel-T appeared to be generally safe and well tolerated by patients with metastatic AIPC. Detailed review on safety can be seen in the medical reviewer's memo.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

No subgroup analysis was conducted for gender since the product is indicated for the treatment of **men** with metastatic AIPC.

Overall survival results from subgroup analyses of age and race for Study D9902B (relatively large size) are presented in Figure 3 of this review memo. Since the BLA contains data from three randomized trials (127 patients in Study D9901, 98 patients in Study D9902A, and 512

patients in Study D9902B), this reviewer also combined all data from the three randomized trials and conducted subgroup analyses. As indicated in Table 10 below, patients randomized to Sipuleucel-T showed a numerical improvement in overall survival compared to those randomized to placebo in all subgroups. The improvement in the Caucasian, African American, and older patients (≥ 65) was statistically significant. However, the numerical improvement in patients with age less than 65 was minimal.

Table 10 Subgroup Analysis of Overall Survival by Age and Race

	Sipuleucel-T		Placebo		Sipuleucel-T vs. placebo
	N	Median Survival (95% CI)[1]	N	Median Survival (95% CI)[1]	Hazard Ratio (95% CI)[2]
Age					
< 65	106	29.0 (22.8, 34.2)	66	28.2 (23.4, 32.5)	0.919 (0.618, 1.366)
≥ 65	382	23.4 (22.0, 27.1)	183	17.3 (13.5, 21.4)	0.661 (0.538, 0.813)
Race					
Caucasian	437	24.6 (22.3, 27.1)	229	21.6 (17.7, 23.6)	0.771 (0.637, 0.937)
African American	33	45.3 (23.4, 46.2)	10	14.6 (10.2, 17.3)	0.271 (0.109, 0.673)
Others	18	32.6 (15.8, ….)	10	26.2 (21.4, 35.6)	0.663 (0.224, 1.961)

[1] Based on a Kaplan-Meier estimate (in months).
[2] HR estimated based on Cox model with treatment as independent variable, stratified by study.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

Data to support the efficacy of Sipuleucel-T for the treatment of men with metastatic AIPC were provided from the randomized, double blind, placebo-controlled, multi-center Phase 3 studies D9902B, D9901, and D9902A that enrolled a total of 737 patients. Table 11 shows the key efficacy results of the overall survival for the individual studies (D9902B, D9901, and D9902A) and the integrated analysis by pooling all data from the three studies together. A statistically significant improvement in overall survival was observed in Studies D9902B and D9901 though the test of overall survival for Study D9901 was not a pre-specified primary endpoint. A trend towards improvement was observed in Study D9902A. Integrated analysis supports the finding of improvement in overall survival.

Table 11 Summary of Overall Survival Analysis Results

	Sipuleucel-T		Placebo		Sipuleucel-T vs. placebo	
	N	Median Survival[4]	N	Median Survival[4]	Hazard Ratio (95% CI)	p-value
D9902B (N=512)[1]	341	25.8	171	21.7	0.775 (0.614, 0.979)	0.032
D9901 (N=127)[2]	82	25.9	45	21.4	0.586 (0.388, 0.884)	0.010
D9902A (N= 98)[2]	65	19.0	33	15.7	0.786 (0.484, 1.278)	0.331
Integrated Studies (N=737)[3]	488	25.4	249	21.5	0.734 (0.612, 0.881)	0.0009

[1] Hazard Ratio (HR), confidence interval (CI) and p-value estimated according to the primary analysis methods.
[2] HR, CI and p-value estimated based on unadjusted Cox model and log rank test as presented in the individual clinical trial report.
[3] HR, CI and p-value estimated based on Cox model with treatment as independent variable, stratified by study.
[4] Based on a Kaplan-Meier estimate (in months).

No differences between the two study arms were observed in time to objective disease progression, progression free survival, time to clinical progression, and time to prostate-specific antigen (PSA) doubling time. Immune response samples were only collected from a subset of the study population in which, the Sipuleucel-T treated group exhibited some immune-specific responses post-treatment.

An improvement in overall survival is the primary evidence of efficacy. The major concern for the observed improvement in overall survival is that the survival difference between the two arms may be attributable to the post-treatment of docetaxel, the only treatment in metastatic castration resistant prostate cancer with a known survival benefit.

In Study D9902B, more patients in the Sipuleucel-T arm received docetaxel following study treatment, as compared to the placebo arm. The median time from randomization to post-treatment docetaxel use in the Sipuleucel-T arm was shorter than that in the placebo arm.

However, the analyses of docetaxel treatment following randomization did not show that the survival difference between the two arms was attributable to the post-treatment of docetaxel. In Study D9901, more patients in the placebo arm were treated with docetaxel following disease progression, compared to the Sipuleucel-T treated patients. The impact of docetaxel treatment following disease progression on survival should be in direction against the claim of Sipuleucel-T benefit if there is a docetaxel treatment benefit in Study D9901.

Sipuleucel-T, an autologous active cellular immunotherapy product, appeared to be generally safe and well tolerated by patients with metastatic AIPC.

4.2 Conclusions and Recommendations

The large randomized, double-blind, well-controlled Phase III study (D9902B) demonstrated that patients with metastatic AIPC who received Sipuleucel-T had improvement in overall survival, compared with those who received placebo. The finding was also supported by the other two small randomized trials (D9901, D9902A). Sipuleucel-T appeared to be generally safe and well tolerated by patients with metastatic AIPC.

The efficacy results from the three randomized trials support the claim of using Sipuleucel-T for the treatment of men with asymptomatic or minimally symptomatic metastatic AIPC.

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APPENDIX: PREVIOUS STATISTICAL REVIMW MEMO